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Disparities in hemodynamic resuscitation of the obese critically ill septic shock patient☆

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ABSTRACT

Background: With a growing obesity epidemic, the approach to care of this patient remains controversial and in many circumstances different than the general population. Appropriate hemodynamic support, although still controversial, remains a cornerstone of septic shock therapy. Catecholamines are currently recommended by guidelines without a preferred dosing strategy. However, the use of weight-based ($\mu g\ kg^{-1}\ min^{-1}$) or nonweight-based (μg/min) vasopressor drip rates may impact patient care in these populations.
Methods: A multicenter retrospective chart review was conducted. Patients receiving nonweight-based catecholamine infusions for septic shock were grouped into nonobese (n = 112) or obese (n = 196), and evaluated based on hemodynamic resuscitation. For the primary outcome, groups were analyzed for the requirement of a secondary hemodynamic support agent to obtain a goal mean arterial pressure of greater than or equal to 65 mm Hg. Secondary outcomes included an evaluation of time to a secondary hemodynamic support agent, time to hemodynamic stability (HDS), ability to obtain HDS at 24 hours, and death due to cardiovascular collapse.
Results: With the exception of weight and sex, baseline characteristics were similar among groups. Early resuscitative fluids were given at a lower weight based, but not total volume dose in the obese group (nonobese, 34.8 mL/kg vs obese, 22.4 mL/kg; $P < .0001$). The primary end point of addition of any secondary hemodynamic support agent was significantly greater in obese patients when adjusted for institution (nonobese, 19% vs obese, 27%; adjusted odds ratio, 0.42; 95% confidence interval, 0.23-0.77). Time to HDS was also prolonged (nonobese, 3.5 hours vs obese, 5.3 hours; $P = .006$).
Conclusion: This study calls into question the adequacy of a nonweight-based approach to hemodynamic support of critically ill obese patients. This strategy seems to result in less aggressive, lower weight-based vasopressor and fluid doses, and more diverse approach than their nonobese counterparts.

1. Introduction

Septic shock is a leading cause of hospital admissions in the United States and is among the top 5 causes of hospital death, with mortality rates as high as 50% [1,2]. The Surviving Sepsis Campaign advocates for aggressive fluid resuscitation followed by vasopressor therapy for refractory hypotension in all patients to maintain an early, within initial 6 hours, target mean arterial pressure (MAP) of 65 mm Hg [1]. Failure to meet hemodynamic goals has been associated with impairment of oxygen delivery, increased organ failure, and mortality [3]. Thus, supporting the importance of early goal directed therapy and timely achievement of blood pressure goals to ensure optimal patient outcomes.

Today, nearly a quarter of patients in intensive care units (ICUs) meet criteria set by the World Health Organization for obesity [4]. Evidence in critically ill obese patients suggests an association with increased hospital admissions, longer length of stay, and 46% higher inpatient costs [5-7]. Initial data indicate that obesity is a risk factor for the development of sepsis and may lead to worse outcomes when compared with nonobese patients [8-10]. Alterations in pharmacokinetic properties in the overweight and obese have proven to be challenging when dosing a number of medications [11,12]. Literature evaluating critically ill obese patients still remains scant, limiting the guidance on appropriate care and dosing of medications in this population. Obese patients are not only at risk of receiving lower total doses of medications, such as vasopressor agents, but also smaller weight-based fluid volumes [3,10,13,14]. Nonweight-based

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dosing (μg/min) is common at many institutions for catecholamines, including norepinephrine, epinephrine, and phenylephrine, failing to take into account patient weight. This strategy, in conjunction with institutional maximum doses, may fail to account for alterations in pharmacokinetics, potentially leading to increased time to goal MAP, failure to achieve early response, and the addition or combination of hemodynamic support agents less commonly seen in the nonobese patient.

A number of observational and randomized controlled trials, examining the resuscitation of septic shock patients, have identified differences in the care of the obese population [13,14]. The true impact of obesity on care and outcomes of critically ill patients still remains controversial. Past evidence in critically ill obese patients has identified alterations in overall care, higher rates of nosocomial infection, and prolonged ICU lengths of stay [19-22]. These patients commonly receive therapies that differ from the nonobese population; however, outcomes to date have not definitively been worse, and in some circumstances appear to be better [20,22]. Therapeutic approaches such as use of nonweight-based dosing (μg/min) or weight-based dosing (μg kg^{-1} min^{-1}) of catecholamines and the impact on care remain unanswered [3,15-18].

The purpose of this study was to determine if the use of nonweight-based dosing impacted the early resuscitation strategies in obese (body mass index [BMI], ≥30 kg/m^2) septic shock patients resulting in increased use of alternative therapies to obtain hemodynamic goals, maintain hemodynamic goals, and increased time to hemodynamic stability (HDS) compared with nonobese (BMI, <30 kg/m^2) patients.

2. Methods

A multicenter, retrospective chart review was conducted at 2 institutions. These institutions included 1 695-bed academic center with more than 100 adult ICU beds and a 528-bed not-for-profit community hospital with more than 40 ICU beds. The study protocol was institutional review board approved at both institutions, and a waiver of informed consent was obtained due to the retrospective nature. Patients 18 years or older receiving a nonweight-based norepinephrine, phenylephrine, or epinephrine continuous infusion between October 1, 2010 and October 15, 2014 were identified and randomly reviewed for inclusion/exclusion criteria. Patients were included if vasopressors were initiated with nonweight-based dosing, after administration of intravenous fluids, for septic shock per physician diagnosis. Patients were excluded for pregnancy, missing data, indication other than septic shock, or documented cardiac arrest within previous 24 hours. Subjects were grouped into nonobese (BMI, <30 kg/m^2) or obese (BMI, ≥30 kg/m^2) for initial analysis. For patients who were readmitted to the ICU during a single hospital stay or during the study period, only data from the first ICU stay were collected. Because of the retrospective design, the titration of vasopressors was based on institutional practices of the pharmacy and nursing staff. Vasopressor titrations were done to achieve HDS in a method that is commonly seen in practice complying with international guideline recommendations of achieving an early MAP goal of greater than 65 mm Hg [1]. The decisions to implement a second therapy or choice of secondary agent were left to the discretion of the treating physician.

The primary outcome was the occurrence of a therapeutic failure in which the addition of a secondary hemodynamic support agent, to obtain the hemodynamic goal of a MAP greater than or equal to 65 mm Hg, was required in obese vs nonobese patients with septic shock. Patients were considered meeting the primary end point in the event the secondary hemodynamic agent was added to obtain a MAP of greater than 65 mm Hg. Secondary outcomes included an evaluation of time to the administration of a secondary hemodynamic support agent, time to HDS, ability to obtain HDS at 24 hours, and death due to cardiovascular collapse. Groups were evaluated based on the total number of hemodynamic agents required, and finally, requirement of an additional agent(s) to maintain hemodynamic goals.

For purposes of this study, a *secondary hemodynamic agent* was defined as the addition of a catecholamine (norepinephrine, epinephrine, or phenylephrine) or vasopressin. Hydrocortisone was only considered in the total number of hemodynamic support agents, not in the secondary agents due to onset of effects. *Hemodynamic stability* was defined as a MAP greater than or equal to 65 mm Hg for 2 consecutive hours. *Death due to cardiovascular collapse* was defined as death before cessation of catecholamine support or within 24 hours of initiation.

For primary and secondary end points, the following were collected: type, rate, and duration of initial and subsequent vasopressor infusions administered; total amount of fluid boluses (milliliter per kilogram) administered in the 24 hours preceding vasopressor initiation; and calculated time to obtainment of goal MAP and sustained goal MAP. Infusion rates and fluid boluses were recorded as standard and weight-adjusted rates by using total body weight for calculations, these were then documented in μg kg^{-1} min^{-1} and mL kg^{-1} day^{-1}.

2.1. Statistical analysis

To assess statistical significance, an estimated need for a secondary hemodynamic support agent of 30% in the obese and 20% in the nonobese arm was assumed. With an α of less than or equal to .05 and power set to 80%, it was determined that 150 patients were needed in each group. Continuous variables were summarized using means ± SDs, and analyzed using Wilcoxon rank sum test. Categorical variables were described using counts and percentages, and analyzed using Fisher exact tests or Pearson χ^2 test. Logistic regression was used to model the probability that an additional agent would be required to reach goal MAP. Only baseline variables that differed significantly between weight categories were included in the initial model. The best subset selection method was performed to assess the best predictive model. This method finds the best model containing all of the given independent variables. The criterion used to determine the "best" subset was based on the global score χ^2 statistic. For 2 different models, each having the same number of explanatory variables, the model with the higher score χ^2 statistic was considered to be better.

3. Results

Nine hundred ninety-four patients were reviewed. Of these, 681 patients were excluded for various reasons. The most common reason for exclusion was missing resuscitation data from the electronic medical record, including amount of fluid administered, time and dose of administered vasopressors, and hemodynamic parameters during the

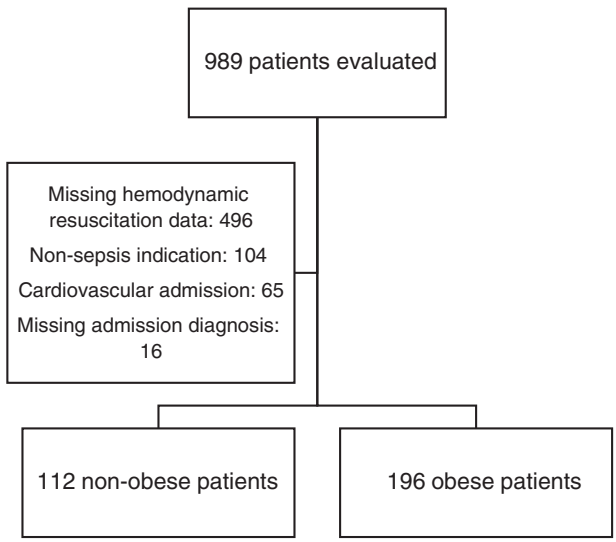

Fig. 1. Patient inclusion.